BIOLOGICAL MARKERS IN CHILDREN WITH IRON DEFICIENCY

The purpose of this study was to determine the effect of iron deficiency on measures of the TH1, TH2 and innate immune responses of children. The hypothesis was that iron deficiency may enhance the TH1 and innate immune responses. In 70 Zimbabwean children <5 years of age studied at well-child clinics, iron status was determined by measuring serum concentrations of transferrin receptor (TFR) and ferritin (FTN), and taking the ratio of TFR/log10 FTN to define iron deficiency. Serum levels of the TH1 immune markers interleukin (IL)-12, interferon-γ (IFN-γ) and inducible protein-10 (IP-10), the TH2 cytokines IL4 and IL10 and the innate immune response cytokine tumor necrosis factor-α(TNF-α) were compared according to the presence or absence of iron deficiency in analysis of variance models that adjusted for age and the Q248H mutation in ferroportin. Fourteen of the children had iron deficiency. Serum concentrations of IP-10 (P =.029) and TNF-α (P=.005), but not the other immune markers, were significantly lower in the children with iron deficiency. Most of the children did not have measurable levels of IL-12 and IFN-γ, but all of those who did (four in the case of IFN-γ and 3 in the case of IL-12) were not iron deficient. The results of this study are consistent with the possibility that iron deficiency is associated with decreased production of TH1 and innate response immune molecules.

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INTRODUCTION

Iron deficiency can be caused by insufficient dietary iron or blood loss. Children five years of age or younger often become iron deficient because of inadequate dietary iron for rapid growth. Immune responses might be affected by this problem. Cellular iron homeostasis affects immune function,[1] and both iron deficiency and iron overload seem to alter the proliferation of T- and B-lymphocytes.[2,3] Increased intracellular concentrations of non-ferritin bound iron reduce the effect of IFN-γ on mononuclear–phagocytes.[4] The withdrawal of iron from cells of the mononuclear–phagocyte system by the application of the iron chelator, desferrioxamine, stimulates the metabolic pathways induced by IFN-γ.[4] A prevalent mutation in the population of Zimbabwe is the Q248H mutation in ferroportin, a protein that exports iron from enterocytes and macrophages.[5] This polymorphism seems to be associated with higher iron stores in adults. The aim of this study was to see if there is a connection between iron status (whether or not the children are iron deficient) and immune function. We hypothesized that the children with iron deficiency may have enhanced TH1 and innate immune responses. We compared markers of the TH1, TH2 and innate immune responses according to iron status in analysis of variance models that adjusted for age and the Q248H mutation in ferroportin.

METHODS

This study was conducted after obtaining institutional review board approval and written informed consent was obtained for each participant. Infants and preschool children attending well-child clinics in Harare, Zimbabwe were studied. Blood samples were obtained for measuring serum or plasma concentrations of ferritin, transferrin receptor, and immune molecules and for isolating DNA to test for the Q248H mutation in ferroportin. Iron deficiency was defined as a transferrin to log10 ferritin ratio of greater than 8.5. The data was analyzed with the Systat statistical program. After exploratory analyses, analysis of variance was used to compare the levels of immune markers according to iron status in models that adjusted for age and the Q248H mutation in ferroportin. The immune markers included IL-12, IFN-γ, and IP-10 of the TH1 response, IL-4 and IL-10 of the TH2 response, and TNF-α of the innate immune response.

RESULTS

Fourteen (25%) of the children had iron deficiency. Children with iron deficiency were significantly younger than those without iron deficiency. A lower proportion of the iron deficient children had the ferroportin Q248H mutation, but this difference was not statistically significant. Serum concentrations of C-reactive protein (CRP) did not differ significantly between the two groups. Plasma concentrations of IP-10 (P=.029) and TNF-α (P=.005), but not the other immune markers, were significantly lower in the children with iron deficiency. Most of the children did not have measurable levels of IL-12 and IFN-γ, but all of those who did (four in the case of IFN-γ and 3 in the case of IL-12) were not iron deficient. (Table 1)

Table 1. Demographic variables, measures of iron status and immunologic markers according to presence or absence of iron deficiency

	Iron deficient (*n*=14)	Not iron deficient (*n*=56)	*P* value
Age (months)*	18 +/− 9	31 +/− 15	<.0005
Female	5 (36%)	27 (48%)	.551
Ferroportin Q248H	1 (7%)	13 (25%)	.269
Hemoglobin (g/dl)*	10.2 +/− 1.7	11.1 +/− 1.1	.079
Hematocrit (%)*	31.6 +/− 4.0	33.0 +/− 3.5	.26
Mean corpuscular volume (fl)*	69.9 +/− 9.2	76.5 +/− 7.5	.029
Ferritin (g/l)**	6 (4–8)	25 (12–64)	.000
Transferrin receptor*	13.5 +/− 6.1	6.5 +/− 1.7	.001
CRP*	1.7 +/− 4.0	2.5 +/− 3.9	.512
TH1 markers			
IL-12**	.5 (.4–.6)	.6 (.5–.6)	.605
IFN-**	.6 (.5–.8)	.9 (.8–1.0)	.258
IP-10**	55.8 (37.1–84.1)	159.6 (130.9–194.5)	.029
TH2 markers			
IL4**	11.9 (5.8–24.5)	11.6 (8.2–16.5)	.977
IL10**	2.1 (1.3–3.4)	6.1 (4.8–7.8)	.058
Innate immune marker			
TNF alpha**	2.1 (1.3–3.3)	9.6 (7.7–12.0)	.005

* Mean +/− SD
** Geometric mean and SE range

DISCUSSION

The results from this study suggest that iron deficiency does not heighten the immune response, but rather that this condition might actually decrease the levels of certain TH1 and innate immune response markers. Limitations to this study include a small sample size, the fact that HIV status of the children was not determined, and that certain children may have not been classified correctly as to iron status. Although our findings are not in accord with our original hypothesis, they are consistent with some studies reported in medical literature. A review of the literature in 1987 concluded that iron deficiency is associated with abnormalities in cell mediated immunity and ability of neutrophils to kill several types of bacteria.[6] More recently, iron deficiency in mice has been associated with reduced levels of IL-12 and IFN gamma.[7]

CONCLUSION

The results of this project add to the literature suggesting that the immune response may be impaired in the setting of iron deficiency. In view of the magnitude of the problem of iron deficiency in the world's children, our findings underscore the importance of strategies to prevent this nutritional deficit. Furthermore, a larger study to followup on these findings may be indicated.

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